Research Strategies and Critical Data Needs

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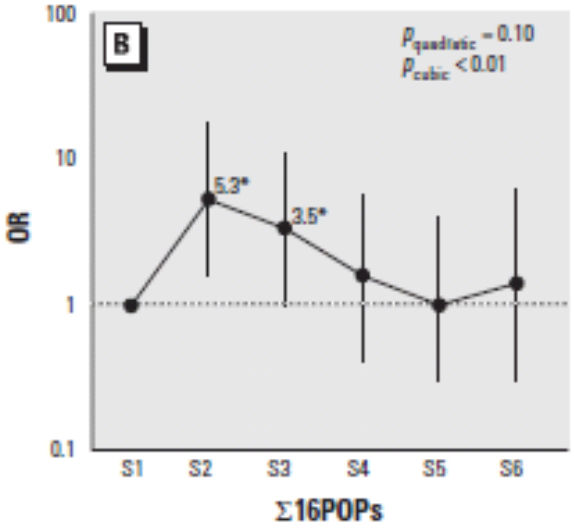
Figure B. Adjusted ORs and 95% CIs of incident diabetes (years 2-20) according to sextiles of serum concentrations ranks of *16 selected POPs [Σ16POPs: 3 OC pesticides + PBB153 + 12 PCBs) with ORs ≥ 1.5 in their second quartile. Adjusted for age, sex, race, BMI, triglycerides, and total cholesterol at year 2.*

Figure C. Year 2 BMI < 30 kg/m²

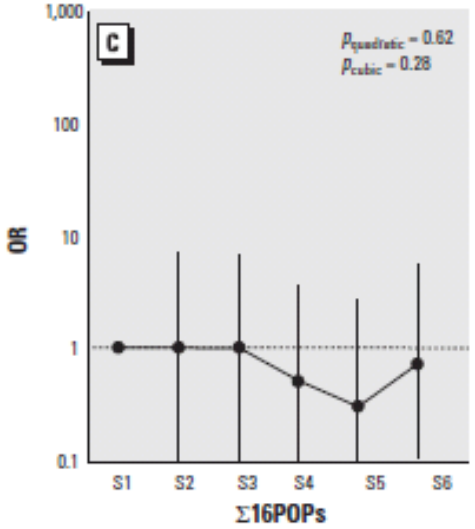
Figure D: Year 2 BMI ≧ 30 kg/m²

90 cases and 90 controls

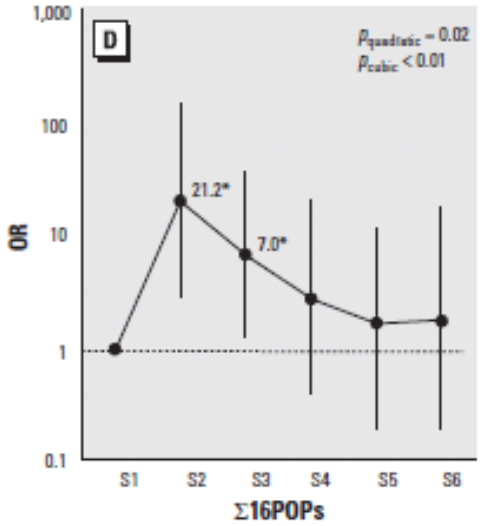
All



Non-obese



Obese



Lee et al. Low Dose of Some Persistent Organic Pollutants Predicts Type 2 Diabetes: A Nested Case–Control Study *Environ Health Perspect (2010).*

Sir A. Bradford Hill. The Environment and Disease: Association or Causation? Proc Royal Soc Med 1965

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Bradford Hill Criteria for Inferring Causality in Epidemiologic Studies

1. Strength of Association
2. Consistency
3. Specificity
4. Temporality
5. Biological Gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Application to POPs and Diabetes

1. **Strength of Association**: Yes
2. **Consistency**: Several studies in different setting, but different POPs show up in different studies and geographic settings
3. **Specificity**: Broad effect (not considered a strong criterion)
4. **Temporality**: Yes, prospective studies (small lingering doubt that early dysmetabolism might impair ability to process POPs)
5. **Biological Gradient**: Strong, but often U-shaped, consistent with known behavior of endocrine disrupting compounds
6. **Plausibility**: Yes, compounds that are toxic to one life form (eg pesticides) are not likely to have no effect in another
7. **Coherence**: Consistent with biologic concepts and time trends
8. **Experiment**: Probable, similar dysmetabolic effects seen in experiments in animals
9. **Analogy**: Similar findings in diabetes precursors

Needs

1. More Epidemiologic Data
    1. There are many epidemiologic studies with stored samples waiting for POPs measurements (and other environmental pollutants)
    2. Expand data base by many times
    3. Waiting for less expensive, less sample demand (0.5 ml samples)
2. Which POPs in which settings?
3. Mixtures
4. Non-monotonic dose response
5. Knockout models for specific pathways or other features amenable to cell or animal models
6. Criteria for safe compounds (both new and persisting)